REMARKS

Claims 1-6 and 8-32 are pending in the application. Claims 8-19 were withdrawn from consideration, leaving claims 1-6 and 20-32 subject to examination. Claims 1-6 and 20-32 were rejected under 35 U.S.C. § 112, first paragraph (enablement and written description), and claims 1-6, 20, 21, and 23-31 were rejected under 35 U.S.C. § 102(a). Each of the rejections is addressed below.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-6 and 20-32 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. In addition, these claims were rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description, as well as for including new matter. These rejections are respectfully traversed for the reasons set forth below.

New matter

Applicants first address the new matter rejection. In response to Applicants' prior submission on this matter, the Examiner states that there is no support for the phrase "may have or be at risk of developing." Applicants respectfully disagree. In view of the rejections in this and the parent application, Applicants amended claim 1 to include as an option determining whether a test subject may have or may be at risk of developing a titin-related disease or condition, so that the claim would not require an absolute diagnosis, which the Examiner seemed to be requiring based on the presence of claim terms such as "has or is at risk of developing..." Applicants again submit that the prior amendment to claim 1 is supported on page 7, lines 1-3,

where it is stated that, using the claimed method, "it is possible to detect an increased likelihood of heart disease..." (emphasis added). Applicants respectfully submit that if an increased likelihood of heart disease is detected in a subject, this means the same thing as a statement that the subject *may* develop heart disease.

The above notwithstanding, Applicants have amended claim 1 herein to specify that the test subject "has an increased likelihood of developing a titin-related disease or condition of the heart," instead of "may have or be at risk of developing" such a disease or condition. The amendment is supported at page 7, lines 1-3. Applicants also make note of claim 20, which has been amended to specify that the method of claim 1 is carried out to detect such an increased likelihood. In view of the above, Applicants request that the new matter rejection be withdrawn.

Enablement

In response to Applicants' previous submission with respect to the prior amendment of the claims to specify a "naturally occurring titin gene," the Examiner states that this phrase encompasses titin genes from any species, and thus includes an extremely large number of possible allelic variants, homologs, and mutants. In response, and in the interest of expediting prosecution, Applicants have amended the claims herein to specify a naturally occurring human titin gene.

The Examiner further states that "the scope of the instantly pending claims sets forth that any mutation in the titin gene from any source is diagnostic for or predictive of disease risk, or provides information regarding etiology of any heart disease or condition" and that "the scope of the teachings in the specification is not commensurate in scope with the claimed invention, as the

specification provides no teaching or guidance as to which specific mutations in titin from any species, including humans, is associated with a titin related disease or condition of the heart."

In response, Applicants note that the claims now specify analysis of naturally occurring human titin sequences. Further, Applicants submit that detection of a mutation in a titin gene may certainly provide information as to whether it is possible that the mutation may be related to the etiology of a disease or condition of the heart. If there is no such mutation, then the protein does not likely play a role in the disease or condition. If there is a mutation, it is reasonable to conclude that it may possibly play a role in the disease or condition, because the present invention shows that the titin gene plays an essential role in proper development and functioning of the heart. Even if a particular mutation is determined to not play a role in disease, the detection of the mutation indicates a possibility that a medical professional may wish to have knowledge of and evaluate. Because titin most certainly plays an important role in proper heart function, the presence of mutations in titin sequences (or not) provides valuable information.

Applicants further submit that it is well known in the art that some diseases and conditions require the analysis of numerous parameters to arrive at even a possible diagnosis. The present claims do not specify a method that necessarily leads to an absolute, definitive diagnosis every time it is carried out. Rather, the presently claimed method can be used to identify a factor that may play a role in a disease or condition of the heart. This information can be used in conjunction with the results of other tests to assist in diagnosis. Multiple types of tests are often required in the process of diagnosis, because the complexity of certain diseases may result, for example, in a situation where detection of a positive result in any two of five tests indicates a diagnosis of a disease or condition. The method of the present invention could be

used in the context of such a diagnosis, as it certainly would provide information as to whether there is a mutation in a gene important for proper heart function.

With respect to the prior cited Itoh-Satoh reference, the Examiner states that this paper shows that "associating any mutation in the titin gene with any disease or condition of the heart, risk of disease or condition, as well as facilitating the etiology of any disease or condition of the heart, is unpredictable." In response, Applicants submit that, although Itoh-Satoh may indicate that this matter is complex, it is clear that the paper teaches that mutations in titin play a role in cardiomyopathy. This is shown, for example, in the title of the paper: "Titin mutations as the molecular basis for dilated cardiomyopathy." The fact that some mutations in titin may not play a role in disease does not negate the fact that other titin mutations may have such roles. Given the importance of titin to proper heart function, as discovered by the present Applicants, analysis of titin sequences for mutations would appear to be an important step in characterizing a heart condition. This is not negated by the fact that this process may be complicated by the possibility of mutations that do not have an effect.

With respect to the prior cited Siu reference, the Examiner states that this paper shows that those of skill in the art "would not be able to predict which mutations were associated with, or indicative of risk or likelihood of a heart disease or condition or would facilitate in determining the etiology of an existing heart condition." In response, Applicants note that teaching of particular diagnostic mutations is not required, as those of skill in the art can readily analyze sequences from many people to determine which mutations may correlate with disease. The critical teaching of the present application is the connection between titin mutations and proper functioning of the heart. With this information and the available sophisticated sequencing

technologies, those of skill in the art could identify particular mutations of relevance, without undue experimentation.

The Examiner further states in this rejection that a universal correlation need not exist, and that "the specification has not established that one exists so that the skilled artisan would be able to predictably determine that the mere presence of a mutation in titin would indicate that the subject had, was at risk, may have, may be at risk, had an increased likelihood of developing any titin related disease or condition of the heart, or that the mere detection of a mutation in titin would facilitate in determining the etiology of an existing heart condition." Applicants respectfully disagree.

A correlation between a titin mutation and proper heart function has clearly been established in the present application. Detection of a mutation in titin thus provides a basis for concluding that the mutation may play a role in a disease or condition of the heart. The fact that some mutations do not play such a role does not mean that the existence of another mutation cannot be used as a factor in determining whether the other mutation plays a role in a particular disease or condition of the heart. Whether a mutation is present in titin certainly provides information as to whether such a mutation may play a role in the etiology of a disease. If there is no mutation, then it can reasonably be concluded that titin does not play a role. If there is a mutation, then this possibility certainly exists and the existence of the mutation can be viewed as a factor in determination of the etiology of the disease or condition.

With respect to the indication of heart failure (see claim 6), the Examiner states on page 14 of the Office Action that although weak heart beat, as observed in the zebrafish model of the present invention, may lead to heart failure, other causes for heart failure also exist (e.g.,

coronary artery disease, hypertension, and diabetes), and that a mutation associated with any one of these risk factors is not necessarily diagnostic of another. In response, Applicants note that they are not claiming methods concerning all possible causes of heart failure. Rather, claim 1, from which claim 6 depends, specifies that the subject disease or condition is titin-related. Thus, if heart failure (or another disease or condition of the heart) is not related to titin, then it is not related to the present claims.

Applicants further would like to reiterate that support for the fact that carrying out the methods of the present claims would not have required undue experimentation can be found in the Itoh-Satoh et al. (Biochem. Biophys. Res. Com. 291:385-393, 2002) paper cited by the Examiner. As was stated in the prior filed reply, this paper describes a study in which the occurrence of dilated cardiomyopathy (DCM) was correlated with three mutations in the titin gene. One titin polymorphism, Arg328Cys, present in DCM patients was also present in healthy control subjects, but this finding does not negate the fact that detection of mutations in titin can be correlated with disease and conditions of the heart without undue experimentation, because it was simple for Itoh-Satoh to determine the relevance of this mutation to DCM by analysis of control sequences. This paper therefore supports the importance of the titin gene in heart disease, as was first discovered by the present Applicants, and also shows that characterization of mutations in titin does not require undue experimentation.

Applicants also remind the Examiner that new claims 21-32, which specify a method for determining whether a subject may have an increased likelihood of a heart disease or condition, or for facilitating determination of the etiology of an existing disease. These methods do not require an absolute diagnosis, as it appears the Examiner still requires for the method of claim 1.

Rather, these methods can be used, possibly in combination with other methods, to provide an assessment of a subject as to their likelihood of having a heart disease or condition. Applicants request consideration of these new claims.

Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph for lack of enablement be withdrawn, because undue experimentation is not required for those of skill in this art carry out the claimed invention, as is discussed above.

Written Description

Claims 1-6 and 20-32 were also rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. This rejection is respectfully traversed.

In response to Applicants' prior amendment to have claim 1 specify a "naturally occurring titin gene," the Examiner states that this term encompasses titin genes from any species. In response, Applicants note that, as discussed above and in the interest of expediting prosecution, claim 1 has been amended herein to specify that the subject titin gene is a human gene.

The Examiner further notes that the specification has taught only a single human titin nucleic acid and a mutation characteristic of a weak heartbeat in zebrafish, and that the single mutation is not representative of the large genus of possible diagnostic or risk-associated mutations in titin. In response, Applicants note that it is not necessary to have described additional particular mutations, as a reference sequence to compare a test sequence to is provided in the application, and those of skill in the art could readily determine whether a test sequence differs from the reference sequence without undue experimentation. Further, as stated by the

Examiner, there are a large number of possible diagnostic or risk-associated mutations. These do not have to be specifically described, as they could be identified by comparison to naturally occurring human sequences. The fact that the precise position of the zebrafish mutation is not provided does not matter, as it is not required for comparison of human test sequences to human reference titin sequences to detect mutations.

In view of the above, Applicants request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102(a)

Claims 1-6 and 20-31 were rejected under 35 U.S.C. § 102(a) as being anticipated by Satoh et al. (Biochem. Biophys. Res. Com. 262:411-417, 1999). In response to Applicants' prior submission with respect to the Declaration of inventor Xiaolei Xu, the Examiner stated that no declaration was submitted and that if the declaration is to be relied upon, a copy must be submitted. In response, Applicants submit herewith a copy of the Declaration to be made of record in this case. In this Declaration, Applicants established a connection between a mutation causing a weak heartbeat and the titin gene, and thus reduced the present invention to practice, prior to the publication date of the Satoh reference. Accordingly, Applicants respectfully request that the rejection over the Satoh reference be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges not covered or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: July 16, 2007

Susan M. Michaud, Ph.D.
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045